Supreme Court, U.S.
FILED
MAR 13 1996
CLERK

(9) (10)

Nos. 95-754 and 95-886

IN THE

Supreme Court of the United States

OCTOBER TERM, 1995

MEDTRONIC, INC.,
Petitioner and Cross Respondent,

v.

LORA LOHR and MICHAEL LOHR,
Respondents and Cross-Petitioners.

On Writs of Certiorari to the United States Court of Appeals for the Eleventh Circuit

---

BRIEF OF *AMICUS CURIAE* COLLAGEN CORPORATION IN SUPPORT OF PETITIONER AND CROSS-RESPONDENT MEDTRONIC, INC.

JOE W. REDDEN, JR.
Counsel of Record
KEITH A. JONES
BECK, REDDEN & SECREST, L.L.P.
1331 Lamar Street
Suite 1570
Houston, TX 77010
(713) 659-8140

FREDERICK D. BAKER
KATHLEEN D. PATTERSON
SEDGWICK, DETERT, MORAN & ARNOLD
One Embarcadero Center
16th Floor
San Francisco, CA 94111
Attorneys for Amicus Curiae Collagen Corporation

WILSON • EPES PRINTING CO., INC. - 789-0096 - WASHINGTON, D.C. 20001

BPP

QUESTION PRESENTED

Whether the Medical Device Amendments of 1976 ("MDA") preempts common law tort claims relating to a medical device whose distribution in interstate commerce has been authorized by the Food and Drug Administration pursuant to section 510(k) of the MDA following a determination that the device is substantially equivalent to one already on the market.*

---

* *Amicus curiae* Collagen Corporation has no parent corporation and no non-wholly owned subsidiaries.

TABLE OF CONTENTS

	Page
QUESTION PRESENTED	i
INTEREST OF *AMICUS CURIAE*	i
INTRODUCTION AND SUMMARY OF ARGUMENT	3
ARGUMENT	4
FEDERAL REQUIREMENTS PLACED UPON MEDICAL DEVICES PURSUANT TO THE MEDICAL DEVICE AMENDMENTS OF 1976 PREEMPT STATE LAW	4
A. Requirements Imposed on Medical Devices Found to Be Safe and Effective and Approved for Marketing Pursuant to the PMA Process Have Preemptive Effect	4
1. The FDA imposes detailed and specific requirements on devices approved for marketing under the PMA process	4
2. Preemption appropriately serves to safeguard the integrity of the PMA process	8
B. The 510(k) Process Similarly Results in the Imposition of Comprehensive Federal Requirements Entitled to Preemptive Effect	11
CONCLUSION	13

TABLE OF AUTHORITIES

Cases	Page
Kennedy v. Collagen Corp., 67 F.3d 1453 (9th Cir. 1995), *rehearing denied* January 16, 1996	2, 3
King v. Collagen Corp., 983 F.2d 1130 (1st Cir.), *cert. denied*, 114 S. Ct. 84 (1993)	2
Mitchell v. Collagen Corp., 67 F.3d 1268 (7th Cir. 1995), *petition for cert. filed*, 64 U.S.L.W. 2288 (U.S. Feb. 20, 1996) (No. 95-1323)	2, 3, 9
Stamps v. Collagen Corp., 984 F.2d 1416 (5th Cir.), *cert. denied*, 114 S. Ct. 86 (1993)	2
Statutes & Regulations	
21 C.F.R. § 803.1	6
21 C.F.R. § 807.81(a)	12
21 C.F.R. § 808.1(d)	8, 12
21 C.F.R. 814.20	6
21 C.F.R. § 814.44	6
21 C.F.R. § 814.80	7
21 C.F.R. § 814.84	7
21 U.S.C. § 360c	4, 5
21 U.S.C. 360c-360*l*	1
21 U.S.C. § 360e(a)	5
21 U.S.C. § 360e(b)	5
21 U.S.C. § 360e(c)	2, 6
21 U.S.C. § 360e(d)	6
21 U.S.C. § 360e(e)	7
21 U.S.C. § 360i(b)	6
21 U.S.C. § 360j	5
21 U.S.C. § 360k	2, 3, 8, 12
43 Fed. Reg. 18661 (1978)	9
45 Fed. Reg. 67323 (1980)	9
46 Fed. Reg. 46394 (1981)	2
59 Fed. Reg. 64287 (1994)	11
Miscellaneous	
H.R. Rep. No. 808, 101st Cong., 2d Sess. 25 (1990)	11
H.R. Rep. No. 853, 94th Cong., 2d Sess. 12 (1976)	10
S. Rep. No. 33, 94th Cong., 1st Sess. 18 (1976)	10

IN THE

Supreme Court of the United States

OCTOBER TERM, 1995

Nos. 95-754 and 95-886

MEDTRONIC, INC.,
Petitioner and Cross-Respondent,

v.

LORA LOHR and MICHAEL LOHR,
Respondents and Cross-Petitioners.

On Writs of Certiorari to the United States Court of Appeals for the Eleventh Circuit

---

BRIEF OF *AMICUS CURIAE* COLLAGEN CORPORATION IN SUPPORT OF PETITIONER AND CROSS-RESPONDENT MEDTRONIC, INC.

INTEREST OF *AMICUS CURIAE*

Amicus curiae Collagen Corporation ("Collagen") produces Zyderm® Collagen Implant ("Zyderm"), a prescription-only product used by physicians to treat soft-tissue skin defects. Like the Model 4011 cardiac pacemaker lead at issue in this case, Zyderm has been classified by the Food and Drug Administration ("FDA") as a Class III medical device subject to regulation under the Medical Device Amendments of 1976 ("MDA"), 21 U.S.C. §§ 360c-360*l*. However, the Model 4011 lead and Zyderm took different regulatory paths to the market-

place. The FDA granted the Model 4011 lead premarket clearance pursuant to 21 U.S.C. § 360(k) (the "510(k) process") upon finding that it was substantially equivalent to a device already on the market. Pet. App. 6a. But because no medical device similar to Zyderm had been marketed prior to enactment of the MDA, Zyderm was subject to the stringent premarket approval process under 21 U.S.C. § 360e(c) (the "PMA process"). After a detailed investigation, the FDA found Zyderm to be safe and effective and approved it for marketing. 46 Fed. Reg. 46394 (1981).

Zyderm now has been on the market for 15 years. During this time, some patients treated with Zyderm have sued Collagen, alleging that they suffered injurious adverse reactions. Such plaintiffs typically seek damages under common law theories of negligence and strict liability similar to those asserted by cross-petitioners Lohr against petitioner Medtronic, Inc., in this case. Until quite recently, reviewing courts were unanimous in holding that all or most such state-law based claims against Collagen are precluded by the MDA's preemption provision, 21 U.S.C. § 360k(a), which bars the states from imposing "any requirement" different from or in addition to applicable federal requirements. *See, e.g., Mitchell v. Collagen Corp.*, 67 F.3d 1268 (7th Cir. 1995), *petition for cert. filed*, 64 U.S.L.W. 2288 (U.S. Feb. 20, 1996) (No. 95-1323); *Stamps v. Collagen Corp.*, 984 F.2d 1416 (5th Cir.), *cert. denied*, 114 S.Ct. 86 (1993); *King v. Collagen Corp.*, 983 F.2d 1130 (1st Cir.), *cert. denied*, 114 S.Ct. 84 (1993). Late last year, however, the Ninth Circuit rejected and departed from these holdings. Reasoning that common law tort rules do not impose "requirements" within the meaning of 21 U.S.C. § 360k(a), the Ninth Circuit held flatly that the MDA does not preempt *any* claims rooted in state common law. *Kennedy v. Collagen Corp.*, 67 F.3d 1453 (9th Cir. 1995), *rehearing denied* January 16, 1996. Collagen intends to file a petition for certiorari seeking review of the Ninth Circuit's aberrant decision in *Kennedy*.

Both parties in the instant case have identified *Kennedy* as establishing a circuit conflict warranting review. Pet. 16 n.11; Cross-Pet. 11 n.2, 17 n.11, 20. The Court in this case presumably will resolve this conflict by deciding, as a threshold matter, whether state common law imposes "requirements" within the meaning of 21 U.S.C. § 360k(a). This decision will directly affect the Court's subsequent disposition of *Kennedy*. Furthermore, if the Court concludes in this case that state common law does impose "requirements," the Court will proceed to consider the scope of MDA preemption as applied to claims relating to medical devices cleared for marketing under the 510(k) process. The Court's analysis of this issue also is likely to have a direct or indirect bearing upon cases, like *Kennedy* and *Mitchell*, that deal with claims relating to medical devices found to be safe and effective and approved for marketing under the PMA process. Accordingly, Collagen has an obvious and substantial interest in the outcome of this case, and the parties have consented to the filing of this brief.

INTRODUCTION AND SUMMARY OF ARGUMENT

This brief is narrow in focus. Petitioner Medtronic and various *amici* will demonstrate, *inter alia*, that state common law imposes "requirements" within the meaning of 21 U.S.C. § 360k(a) and that such requirements are different from and in addition to the extensive federal requirements governing Class III medical devices, like the Model 4011 cardiac pacemaker lead, that have been cleared for marketing pursuant to the 510(k) process. Collagen will not burden the Court with redundant argumentation on these points. Collagen believes, however, that it will be helpful to the Court, in considering the issues in this case, to understand not only the 510(k) process but the PMA process as well. This brief discusses the latter process and in doing so seeks to shed light on the matter of MDA preemption generally.

The FDA uses the PMA process to determine the safety and effectiveness of new Class III medical devices. Upon

finding a medical device to be safe and effective pursuant to the PMA process, the FDA approves the device for marketing subejct to detailed and specific requirements relating to, *inter alia*, design, manufacturing, packaging, and labeling. A major purpose of MDA preemption is to prevent the states from second-guessing or undermining this process by attempting to impose different or additional requirements of their own.

The PMA process and the 510(k) process differ, but the end results of the two processes are essentially similar: the FDA permits the medical device to go to market subject to numerous federal requirements in the form of both specific conditions and general regulatory controls. Under the MDA, these requirements have preemptive effect.

ARGUMENT

FEDERAL REQUIREMENTS PLACED UPON MEDICAL DEVICES PURSUANT TO THE MEDICAL DEVICE AMENDMENTS OF 1976 PREEMPT STATE LAW

A. Requirements Imposed on Medical Devices Found to Be Safe and Effective and Approved for Marketing Pursuant to the PMA Process Have Preemptive Effect

1. *The FDA imposes detailed and specific requirements on devices approved for marketing under the PMA process*

New "Class III devices must generally undergo premarket approval (PMA) before the FDA will allow them into the marketplace." Pet. App. 4a. The statutory objective of the PMA process is to ensure that the device affords a "reasonable assurance of safety." 21 U.S.C. § 360c(1)(c). Before the FDA approves a Class III device for marketing pursuant to the PMA process, it must determine that the device is safe and effective with respect to (1) the persons for whose use the device is

intended and (2) the conditions of use prescribed, recommended, or suggested in the labeling of the device. 21 U.S.C. § 360c(2). In making this determination, the FDA weighs any probable benefit to health from the use of the device against any probable risk of injury or illness. *Id.*

The PMA process is not the exclusive means by which Class III medical devices enter the market. The MDA provides three alternative routes to marketability: premarket approval is not required for (1) devices on the market prior to the effective date of the MDA, (2) devices, like the Model 4011 lead at issue in this case, found to be substantially equivalent to a device already on the market, or (3) devices entitled to the investigational device exemption. *See* 21 U.S.C. §§ 360e(b)(1)(A) and (B), 360j(g). But premarket approval is the statutory paradigm, and "the MDA contemplates that most Class III devices will reach the market through the PMA process." Pet. App. 4a; *see* 21 U.S.C. § 360e(a).

The PMA process entails an exhaustive investigation into safety and effectiveness. An applicant who seeks the FDA's approval to market a Class III device must provide:

> (A) full reports of all information, published or known to . . . the applicant, concerning investigations which have been made to show whether or not such device is safe and effective;
>
> (B) a full statement of the components, ingredients, and properties and of the principle or principles of operation of such device;
>
> (C) a full description of the methods used in, and the facilities and controls used for, the manufacture [and] processing . . . of such device;
>
> (D) . . . adequate information to show that . . . such device fully meets [pertinent] performance standard[s] . . .;
>
> (E) . . . samples of such device . . .;
>
> (F) specimens of the labeling proposed to be used for such device; and

> (G) such other information . . . as the [FDA] . . . may require.

21 U.S.C. § 360e(c)(1).

The application for marketing approval also must include *inter alia*, a "general description of the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended," an "explanation of how the device functions, the basic scientific concepts that form the basis for the device, and the significant physical and performance characteristics of the device," and a "description of existing alternative practices or procedures for diagnosing, treating, preventing, curing, or mitigating the disease or condition for which the device is intended." 21 C.F.R. § 814.20(b)(3). In addition, the application must be periodically updated "with new safety and effectiveness information learned about the device from ongoing or completed studies." 21 C.F.R. § 814.20 (e).

A completed application must be reviewed by a panel of experts. 21 U.S.C. § 360e(c)(2). After considering the panel's report and recommendation, the FDA will grant the application only if it finds reasonable assurance that the device is safe and effective, determines that the manufacturing and processing methods and facilities are satisfactory, and concludes that the proposed labeling is not false or misleading in any manner. 21 U.S.C. § 360e(d)(2); *see also* 21 C.F.R. § 814.44.

The FDA actively monitors devices after they have been approved for marketing. Both the manufacturer of the device and the health care providers who use it have a duty to report any information that reasonably suggests the device has caused injury. 21 U.S.C. § 360i(b); 21 C.F.R. § 803.1(a). The manufacturer also must periodically furnish information about "unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device" and "[r]eports in the

scientific literature concerning the device." 21 C.F.R. § 814.84(b)(2). Marketing approval will be withdrawn if the FDA finds, *inter alia*, that the "device is unsafe or ineffective under the conditions of use prescribed, recommended, or suggested in the labeling," that "the application contained or was accompanied by an untrue statement of a material fact," or that the labeling "is false or misleading in any particular." 21 U.S.C. § 360e(e)(1).

Once a medical device has been approved for marketing under the PMA process, it remains subject not only to active monitoring but also to tight regulatory controls. Some of these controls apply across the board to all Class III medical devices. The FDA's regulations relating to good manufacturing practice and labeling, discussed by the Eleventh Circuit in this case, are examples. *See* Pet. App. 30a-33a. Other controls, however, are device-specific, consisting of elaborate restrictions on the manufacture, distribution, and sale of a device after it has been approved for marketing.

A PMA approval order represents a license to market the approved medical device strictly in accordance with conditions specified by the FDA to ensure safety and effectiveness. By regulation, "[a] device may not be manufactured, packaged, stored, labeled, distributed, or advertised in a manner that is inconsistent with any conditions to approval specified in the PMA approval order for the device." 21 C.F.R. § 814.80. In turn, the approval order typically sets forth or incorporates a laundry list of such conditions. The FDA's approval order for Zyderm is a case in point. That order set forth numerous "conditions of approval," including the following:

> *PMA Supplements. Before making any change that may affect the safety or effectiveness* of the device, submit a supplemental PMA for review and approval by FDA. Such changes include, but are not limited to:
>
> (1) new indications for use;

(2) labeling changes;

(3) changes in manufacturing facilities, methods or quality control procedures, and involvement of new subcontractors, suppliers, or distributors;

(4) changes in sterilization procedures;

(5) changes in packaging;

(6) changes in the performance or design specifications, circuits parts, components, accessories, ingredients, or physical layout of the device.

Appendix, *infra*, at 4a (emphasis in original).

This means that Collagen, in producing and selling Zyderm, must adhere to all the specifications in its PMA application relating to indications for use, proposed labeling, manufacturing methods and facilities, sterilization procedures, packaging, ingredients, and performance and design. Other medical devices found to be safe and effective and approved for marketing pursuant to the PMA process are made subject to similar conditions. In this way, the FDA transmutes the specifications in a PMA application into binding federal requirements.

2. *Preemption appropriately serves to safeguard the integrity of the PMA process*

In this case, the Court must construe the MDA's express preemption provision, 21 U.S.C. § 360k(a). That statute provides that a state may not impose any requirement with respect to a medical device "(1) which is different from, or in addition to, any requirement applicable under [the MDA] to the device, and (2) which relates to the safety or effectiveness of the device or to any other matter included in a requirement applicable to the device under [the MDA]." By regulation, the FDA has construed this statute as according preemption "when the [FDA] has established specific counterpart regulations or there are other specific requirements applicable to a particular device under the act." 21 C.F.R. § 808.1(d).

Respondents Lohr argue, with respect to the Model 4011 lead, that there is no federal "requirement" entitled to preemption under the statute so construed. As we show below, that argument is wrong. But is is useful to consider the issue first in the context of a device that has been approved for marketing pursuant to the PMA process. In that context, the existence of federal requirements is plain. In the first place, as the FDA itself has explained, "[f]or a device classified in Class III . . . , the counterpart FDA requirement [is] the requirement that the product have premarket approval." 43 Fed. Reg. 18661, 18664 (1978); *see also* 45 Fed. Reg. 67323 (1980). Thus "the premarket approval process constitutes a 'specific requirement' for purposes of 21 C.F.R. § 808.1(d) and 21 U.S.C. § 360k(a)." *Mitchell*, 67 F.3d at 1279. *See also id.* at n.6. (citing decisions in at least five other circuits reaching the same result). In addition, the comprehensive conditions accompanying a PMA approval order constitute "specific requirements applicable to a particular device." 21 C.F.R. § 808.1(d). Under the statute, these detailed and device-specific requirements also have preemptive effect.

Preemption safeguards the integrity of the PMA process. A PMA approval order represents the FDA's determination, following a lengthy and careful review process, that the approved medical device is safe and effective when manufactured, distributed, and sold in accordance with the conditions set forth therein. The federal regulatory process leading to that determination is both extensive and exhaustive. Once an approval order has been issued, the manufacturer remains subject to continued close federal scrutiny but is free to produce and sell the device without state interference or oversight. In this way, the states are precluded from second-guessing or undermining PMA approval orders.

Congress thereby has struck a balance that avoids both under-regulation and over-regulation. This was by express design. Congress developed the MDA as

> a balanced regulatory proposal intended to assure that the public is protected from unsafe and ineffective medical devices, that health professionals have more confidence in the devices they use or prescribe, and that innovations in the medical device industry are not stifled by unnecessary restrictions.

H.R. Rep. No. 853, 94th Cong., 2d Sess. 12 (1976). Congress intended preemption to play a vital role in achieving this balance.

Congress was fully aware of "the importance of the small innovative manufacturer [like Collagen] in the invention and development of new medical devices and the inability of these firms, because of limited financial resources, to sustain the high level of administrative costs demanded of a highly regulated industry." S. Rep. No. 33, 94th Cong., 1st Sess. 18 (1976). Congress determined that extraordinarily extensive federal oversight is necessary to ensure the safety and effectiveness of newly developed medical devices. But Congress further concluded that an additional layer of state-law requirements would be both unnecessary and counterproductive, noting that "interstate commerce would be unduly burdened" by the imposition of "differing requirements applicable to a medical device . . . by jurisdictions other than the Federal government." H.R. Rep. No. 853 at 45. The broadly worded MDA preemption statute grew out of these concerns. It ensures that firms like Collagen, which have met the burden of demonstrating safety and effectiveness under the PMA process, will be subject only to those regulatory requirements that Congress and the FDA have chosen to prescribe.

B. The 510(k) Process Similarly Results in the Imposition of Comprehensive Federal Requirements Entitled to Preemptive Effect

The Model 4011 cardiac pacemaker lead at issue in this case entered the market via the 510(k) process. The explicit focus of the FDA's inquiry under the 510(k) process is whether the medical device is substantially equivalent to another device already on the market, but this also includes "some inquiry into the safety and effectiveness of [the] new device." 59 Fed. Reg. 64287, 64288 (1994). Although proving substantial equivalence may require the submission and evaluation of considerable data, the FDA's investigation ordinarily is not as exhaustive or demanding as that entailed by the PMA process.

This does not mean that a device cleared for marketing under the 510(k) process is any less safe or effective than one approved under the PMA process. To the contrary, the 510(k) process represents a congressional judgment that if a new device is substantially equivalent to one that has demonstrated its own safety and effectiveness by withstanding the test of time, the new device itself is sufficiently safe and effective to be placed on the market. *See* H.R. Rep. No. 808, 101st Cong., 2d Sess. 25 (1990). At the conclusion of either the 510(k) process or the PMA process, therefore, the medical device that is permitted to enter the market is believed to be both safe and effective.

Moreover, notwithstanding their other differences, the two regulatory processes share at least two crucial similarities. *First*, each process embodies a set of federal requirements that must be met before a device may be marketed. Under the MDA, those federal requirements preempt state laws that would impose different or additional restrictions on marketability. *Second*, as is the case

under the PMA process, the final order clearing a device for marketing under the 510(k) process typically specifies that the applicant may not make any changes in, for example, labeling, manufacturing, or design that might affect safety or effectiveness. *See* 21 C.F.R. § 807.81(a). These conditions on continued marketability, like those contained in the typical PMA approval order, constitute further binding federal requirements. They are "specific requirements applicable to a particular device," 21 C.F.R. § 808.1(d), and as such are entitled to preemption under the MDA.

The MDA preemption statute is broadly worded. The statute expressly preempts competing state requirements relating not only to "safety and effectiveness" but also to "any other matter included in a [federal] requirement." 21 U.S.C. § 360k(a)(2). Thus it is the existence of a federal requirement, not the finding of safety and effectiveness, that triggers preemption under the statute. As petitioner Medtronic will show, the Model 4011 lead is subject to numerous such requirements, including a requirement that there be no change in design affecting safety or effectiveness. Under the MDA preemption statute, the states may not impose different or additional requirements of their own.

CONCLUSION

The judgment of the Eleventh Circuit should be reversed insofar as it allows respondent Lohrs' design claims to go to trial; the judgment otherwise should be affirmed.

Respectfully submitted,

JOE W. REDDEN, JR.
Counsel of Record
KEITH A. JONES
BECK, REDDEN & SECREST, L.L.P.
1331 Lamar Street
Suite 1570
Houston, TX 77010
(713) 659-8140

FREDERICK D. BAKER
KATHLEEN D. PATTERSON
SEDGWICK, DETERT, MORAN & ARNOLD
One Embarcadero Center
16th Floor
San Francisco, CA 94111
Attorneys for Amicus Curiae Collagen Corporation

APPENDIX

APPENDIX

[LOGO]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
8757 Georgia Avenue
Silver Spring MD 20910

[Jul. 22, 1981]

Bruce B. Pharriss, Ph.D.
Vice President of
Scientific Affairs
Collagen Corporation
2455 Faber Place
Palo Alto, California 94303

Re: P800022
Zyderm™ Collagen Implant
Filed: May 2, 1980
Amended: November 10, 1980
February 24, March 19, April 10,
April 16, and May 7, 1981

Dear Dr. Pharriss:

The Food and Drug Administration (FDA) has completed its evaluation of your premarket approval application (PMA) for the Zyderm™ Collagen Implant (hereinafter referred to as Zyderm™). The PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin production and marketing of the device upon receipt of this letter.

FDA will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. In addition, the notice will state that a copy of all approved final labeling (which may be a draft of the final labeling) is available for public inspection at the Bureau of Medical Devices. Within thirty days of publication of the notice of approval in the FEDERAL REGISTER, any interested person may obtain review of this decision by requesting an opportunity for administrative review, either through a hearing or

review by an independent advisory committee under section 515(g) of the Federal Food, Drug, and Cosmetic Act.

FDA approval is subject to full compliance with the conditions described in the enclosure and the following:

1. The sale, distribution, and use of this device is to be restricted to prescription use in accordance with 21 CFR 801.109.

2. The post-approval (Phase IV) studies under your immunology protocol ZC-980 shall be extended from 3 to 12 months, and shall include determination of antibody levels in patients at 6 and 12 months after initiation of Zyderm™ treatment and the results submitted in the annual report. The studies shall report experimental details, such as the frequency and the amount of Zyderm™ injected, and the dates of blood sample collection from each patient. Patients selected under this protocol shall represent a cross section of patients receiving Zyderm™.

   In addition to Zyderm™, native and denatured bovine skin type I collagen (not treated by pepsin) shall be used to determine the levels of anti-Zyderm™ antibodies in the patients.

   Data on the cross-reactivity of Zyderm™ antibodies with type III collagen shall be provided, since human skin contains both type I and type III collagen.

   Circulating Zyderm™-antibody complexes shall be determined in fresh blood samples, and their levels demonstrated to be in the same range as those from individuals not exposed to Zyderm™ treatment.

3. In the post-approval (Phase IV) period, Zyderm™-treated patients shall be monitored for the occurrence of adverse reactions at 6-month intervals during a 3-year period, and the follow-up data submitted in the annual report to the FDA.

   FDA will review these data and determine whether or not the post-approval monitoring of Zyderm™ should be continued at the present level.

4. A patient information manual shall be distributed with the device.

All stated requirements are subject to change upon publication of a final premarket approval procedural regulation. Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a product which is not in compliance with these conditions is a violation of the Federal Food, Drug, and Cosmetic Act.

All required documents must be submitted in duplicate to the Bureau of Medical Devices, Document Control Center (HFK-20), 8757 Georgia Avenue, Silver Spring, Maryland 20910.

If you have any questions concerning the approval of this application or its conditions, please contact Carl A. Larson, Ph.D., at (301) 427-7156.

Sincerly,

/s/ Robert G. Britain
for VICTOR ZAFRA
Acting Director
Bureau of Medical Devices

Enclosure

Conditions of Approval

Approved Labeling. As soon as possible, and prior to commercial distribution of your device, submit two copies of all approved labeling in final printed form.

Advertisement. No advertisement for this device shall recommend or imply that the device may be used for any use that is not mentioned in the approved labeling for the device. All written promotional material shall state the indications, contraindications, warnings, precautions and adverse effects of the device.

PMA Supplements. Before making any change that may affect the safety or effectiveness of the device, submit a supplemental PMA for review and approval by FDA. Such changes include, but are not limited to:

(1) new indications for use;

(2) labeling changes;

(3) changes in manufacturing facilities, methods or quality control procedures, and involvement of new subcontractors, suppliers, or distributors;

(4) changes in sterilization procedures;

(5) changes in packaging; and

(6) changes in the performance or design specifications, circuits parts, components, accessories, ingredients, or physical layout of the device.

Changes in labeling, manufacturing, sterilization, packaging, or performance or design specification which enhance safety of the device or safety in the use of the device may be placed into effect by the sponsor prior to the receipt of a written FDA approval of the supplemental PMA provided:

(1) the submission is plainly marked on the mailing cover and on the supplement "Special PMA Supplement—Changes Being Effected";

(2) the supplemental PMA provides a full explanation of the basis for the changes;

(3) the applicant has received acknowledgement from the Bureau of Medical Devices of receipt of the supplement; and

(4) the supplement specifically identifies the date that such changes are being effected.

Specific examples of changes permitted are:

(1) addition of warnings, contraindications, or side effects;

(2) deletion of misleading, false, or unsupported indications; and

(3) changes in the manufacturing process or quality controls that provide additional assurance of purity, identity, strength, or reliability.

FDA may, as experience permits, issue guidelines listing specific types of changes that do not require FDA approval prior to implementation.

Post-Approval Reports. Continued approval of your device is contingent upon the submission of post-approval reports to the Bureau of Medical Devices at intervals of one year from the date of this letter. The required contents of these reports will be described in the FEDERAL REGISTER in the premarket approval procedural regulation which will be published in the future. Until this regulation is published in final form, each periodic report shall consist of information that previously has not been submitted as part of a PMA or supplemental PMA and which you have obtained since the last post-approval report or since receipt of this letter, whichever is later:

1. A summary and bibliography of reports in the scientific literature involving the device and unpublished reports of *in vitro*, animal and clinical experience studies, investigations, and tests con-

ducted by, reported to, or reasonably available to you involving the device or a related device.

If, after reviewing the summary and bibliography, FDA concludes that it needs a copy of the published and unpublished reports themselves, FDA will notify you that copies of such reports shall be submitted.

2. Written promotional material.

3. A description of changes made in the device not previously submitted in a supplemental PMA.

Adverse Reaction and Device Defect Reporting.

You shall submit a written report to the Bureau of Medical Devices within ten days after you receive or have knowledge of information about:

(1) a mixup of the device or its labeling with another article;

(2) any significant chemical, physical, or other change or deterioration in the device, or any failure of one or more of the devices to meet the specifications established in the application; and

(3) any adverse reaction, side effect, injury, toxicity, or sensitivity reaction or any unexpected incidence, or severity thereof, associated with any clinical use, study, investigation, or test of the device, which has been determined to be attributable to the device or has not been addressed by the device labeling. The term "unexpected" refers to conditions or developments not previously identified in the application.

Note: All conditions of approval are subject to change upon publication of a final premarket approval regulation.